Cancer Incidence Among Those Initiating Insulin Therapy With Glargine Versus Human NPH Insulin

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OBJECTIVE—To add to the evidence on comparative long-term effects of insulin analog glargine versus human NPH insulin on the risk for cancer.

RESEARCH DESIGN AND METHODS—We identified cohorts of initiators of glargine and human NPH without an insulin prescription during the prior 19 months among patients covered by the Inovalon Medical Outcomes Research for Effectiveness and Economics Registry (MORE^2 Registry) between January 2003 and December 2010. Patients were required to have a second prescription of the same insulin within 180 days and to be free of cancer. We balanced cohorts on risk factors for cancer outcomes based on comorbidities, comedication, and health care use during the prior 12 months using inverse probability of treatment weighting. Incident cancer was defined as having two claims for cancer (any cancer) or the same cancer (breast, prostate, colon) within 2 months. We estimated adjusted hazard ratios (HRs) and their 95% CI using weighted Cox models censoring for stopping, switching, or augmenting insulin treatment, end of enrollment, and mortality.

RESULTS—More patients initiated glargine (43,306) than NPH (9,147). Initiators of glargine (NPH) were followed for 1.2 (1.1) years and 50,548 (10,011) person-years; 993 (178) developed cancer. The overall HR was 1.12 (95% CI 0.95–1.32). Results were consistent for breast cancer, prostate cancer, and colon cancer; various durations of treatment; and sensitivity analyses.

CONCLUSIONS—Patients initiating insulin glargine rather than NPH do not seem to be at an increased risk for cancer. While our study contributes significantly to our evidence base for long-term effects, this evidence is very limited mainly based on actual dynamics in insulin prescribing.

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In June 2009, multiple research reports addressed the possibility of association between the use of the long-acting insulin analog glargine (Lantus) and cancer (1–4). This relation was examined because of in vitro observations that glargine is more mitogenic than human insulin; subsequent studies have demonstrated that the in vivo metabolite, which is the dominant circulating form of glargine, is not mitogenic in vitro (5,6). In the original publications as well as further analyses from additional datasets, results have been quite heterogeneous, perhaps related to methodological differences (7–17). The lack of consistent relations with specific cancers has reduced anxiety regarding the potential effect of glargine on cancer. Residual concerns focus on breast cancer, particularly with longer exposure, based on more frequent and stronger associations as well as a general lack of substantial data in that regard (10–12,16). Because glargine is the most commonly prescribed formulation of insulin, its safety is an issue of great clinical and public health interest.

There is a clear association between diabetes and cancer incidence and mortality. The potential drivers of this association are incompletely understood but include insulin resistance and obesity, shared risk factors such as age and smoking, health care system use (i.e., those who are diagnosed with one condition may be more likely to be screened for the other condition), and medication exposure (18,19). Despite the increased incidence of cancer in those with diabetes, cancer events in clinical trials are infrequent. Both a meta-analysis of the glargine clinical trials program and the results of two large safety studies with 5–7 years' follow-up failed to demonstrate any increased risk of cancer or cancer mortality; however, the total number of events in these studies are modest and thus too small to rule out clinically relevant increases in risk, specifically for breast cancer in women (20–22). Additionally, though the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial reported >75,000 patient-years of follow-up, it excluded patients who would meet general indications for insulin therapy. This may limit the generalizability of its conclusions regarding glargine's safety (22).

Therefore, despite the recent boom in studies exploring glargine cancer associations, there is still a need for large pharmacoepidemiologic studies that allow better control for potential confounders as well as analysis of induction periods; namely, how the duration of treatment

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affects the risk observed. This can only be accomplished with a clear time line for the analysis; arguably, the best time line starts with the initiation of insulin therapy (23). We report the largest study to date that addresses these important issues for what we believe to be the most relevant question raised by the June 2009 publications: In patients with diabetes who are initiating treatment with long-acting insulins, how does cancer incidence compare in those initiated on insulin glargine versus NPH insulin, a nonanalog form of insulin with similar indications and clinical effects?

RESEARCH DESIGN AND METHODS

The study was reviewed and determined to be exempt from further review by the University of North Carolina at Chapel Hill Institutional Review Board. The study protocol was registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) electronic register of studies (http://www.encepp.eu/encepp/viewResource.htm?id=2334).

Main study population

The eligible study population consisted of all patients with at least one diagnostic code for diabetes (ICD-9-CM 250.XX) enrolled in a U.S. health plan covered by the Inovalon Medical Outcomes Research for Effectiveness and Economics Registry (MORE^2 Registry) (Bowie, MD) any time between 1 January 2003 and 31 December 2010. The MORE^2 Registry contains data for >76 million patients, 295,000 physicians, and 185,000 clinical facilities and is often able to track patients who change health plans (24). The MORE^2 Registry is comprised of all inpatient and outpatient claims, dispensed prescription medication claims, and mortality data from the Social Security Administration's Death Master File.

We identified the first (if any) dispensed prescription for human NPH or a premixed formulation of human NPH and regular insulin (hereafter collectively referred to as "NPH") or analog insulin glargine after 1 July 2004 (Supplementary Fig. 1)—the index prescription. We then excluded patients without continuous enrollment for 19 months prior to the index prescription, defined as having a claim for any medication during each of four 6-month periods prior to the index prescription. Within this population with active use of drug insurance, we then excluded patients with any dispensed insulin prescriptions in the 19 months prior to the index prescription with the exception of a single prescription for short-acting insulin (animal or human regular insulin or rapid-acting analog insulin). The 19-month period was chosen to represent a usual 30-day supply plus a grace period of 6 months plus a washout period of 12 months.

From our cohort of initiators of long-acting insulin (glargine or NPH), we excluded patients with any evidence of cancer or cancer-related procedures (Supplementary Table 1). This definition was chosen to be as sensitive as possible without implying specificity (i.e., erring on the side of excluding some patients that may not have cancer). We then excluded patients younger than 18 years old at the index prescription.

To increase the likelihood that dispensed insulin was actually used by patients included in the cohort, we further restricted our cohorts to patients with a second prescription for the same insulin (glargine or NPH) dispensed within 6 months after the index prescription. Finally, we excluded patients with any evidence of cancer between the index prescription and the second prescription.

Covariates and control for confounding

All covariates were assessed during the 12 months prior to the index prescription, and all analyses were controlled for a wide variety of variables, including calendar year of initiation, age, comorbidity, number of physician visits, number of hospitalizations, various screenings (mammography, prostate specific antigen, endoscopy), and medications. For a complete list of variables, see Table 1. Using these variables, we predicted the propensity for initiating glargine versus initiating NPH for each patient based on observed covariates (the propensity score) (25). We then created pseudopopulations, weighting each patient's contribution by the inverse probability of receiving the treatment actually received, i.e., inverse probability of treatment weights (IPTW) (26). After checking the maximum weight (7.722) and that the mean weight was close to 1.0 (1.003), which limits the potential for influential patients to bias results, we assessed the balance of observed covariates across treatment cohorts in the pseudopopulations (27). To avoid treatment comparisons outside a common range of the propensity score (and thus possibly covariates), we excluded patients initiating glargine with a propensity score higher than the highest one observed in patients initiating NPH and vice versa.

Cancer incidence

The cancer end points of interest were breast, prostate, colon, and "any" (excluding nonmelanoma skin cancers). These end points were considered separately and defined based on having at least two codes for a specific cancer within 2 months (28). Breast cancer was defined as a primary or secondary diagnosis (ICD-9-CM 174.X or 233.0); prostate cancer (ICD-9-CM 185.X) and colon cancer (ICD-9-CM 153.X) were defined accordingly. Codes used to define "any cancer" are included in Supplementary Table 2.

Patients accrued person-time of follow-up starting from the second prescription until they stopped using the drug (no new prescription for glargine or NPH, respectively, within the recorded number of days' supply plus a 180-day grace period to allow for dose adjustment and irregular use), filled a prescription for another long-acting insulin (all patients were allowed to augment with short-acting insulin), died, or ended enrollment; the study period ended (31 December 2010); or they had a claim for any incident cancer (except nonmelanoma skin cancer). After checking the proportional hazards assumption by adding an interaction term between (log) time and treatment, we then fit Cox proportional hazards models for the various cancer outcomes in the weighted pseudopopulations without controlling for covariates (potentially affected by treatment).

Sensitivity analyses

BMI is associated with an increased risk of some cancers including colon and postmenopausal breast but not prostate cancer (29) and could confound the association between glargine versus NPH initiation and cancer incidence if BMI would affect the choice between initiating these two treatments. To test this possibility, we estimated the association between BMI and choice between initiating glargine versus NPH independent of other covariates, fitting propensity score models equivalent to the one in the main cohort but using two electronic medical record (EMR) databases where information on BMI is available. We used EMR data from the Massachusetts General Hospital (MGH) and from Ochsner. Initiation of

NPH or glargine in the MGH and Ochsner databases was defined as for the Inovalon database; however, only one prescription record from the EMR was required to define initiation, as these databases do not contain a record for dispensing.

Additional sensitivity analyses were performed to enhance the probability of having type 2 diabetes (by restricting cohorts to those >40 years of age and with prior use of oral antihyperglycemic agents), varying induction periods (excluding patients with early cancer diagnosis), varying carryover effects, and excluding increasing proportions of those treated contrary to prediction (i.e., to assess the potential for bias assuming unmeasured confounding [30]).

RESULTS—We present the baseline distribution of covariates in the two cohorts of glargine initiators and NPH initiators in Table 1. Our cohort of patients being initiated on glargine is slightly older, more likely to be male, and more likely to initiate treatment after 2008 than patients initiating NPH (first two columns). The main differences between the treatment cohorts are observed for medication use at baseline. Patients initiating glargine are more likely to have filled prescriptions of antihypertensive, antihyperglycemic, and lipid-lowering drugs. In contrast, patients initiating NPH are more likely to have filled prescriptions for estrogens and progestins. The prevalence of comorbidities is very similar in both cohorts, as is health care use. Patients initiating glargine are more likely to have had a cancer-screening test performed in the year prior to baseline than patients initiating NPH. In the third column, we present the multivariable effect of these covariates on channeling between initiating glargine and NPH (i.e., results from the propensity score model). The virtually identical distribution of the covariates in the propensity score weighted pseudopopulation (last two columns) proves that we were able to balance cohorts on all measured covariates, thus eliminating confounding by these covariates.

In Table 2, we present rates per 100,000 person-years and the crude and adjusted hazard ratios (HRs) for incident cancer for breast cancer (women only), prostate cancer (men only), colon cancer, and "any cancer." All numbers are based on our primary analysis, i.e., as treated, where patients stopping, switching, or augmenting their corresponding baseline treatment are censored at that point in time. The median duration of follow-up in this analysis is 0.9 years in the glargine cohort and 0.8 years in the NPH cohort.

The breast cancer analysis, based on 22,936 patients initiating glargine and 5,536 patients initiating NPH and 122 incident breast cancers, reveals an adjusted HR of 1.07 (95% CI 0.65–1.75). The corresponding HR for prostate cancer (1.19 [0.73–1.94]), colon cancer (0.89 [0.49–1.60]), and any cancer (1.12 [0.95–1.32]) are all close to 1, indicating no increased risk for cancer in glargine initiators compared with NPH initiators.

We then stratified the analysis presented in Table 2 by duration of use since initiation (Table 3). Given the median duration of treatment presented above, there are sparse data for the >24-month strata, especially for the NPH cohort. Based on only 3,415 person-years and 14 incident breast cancers, we found no indication for an increased risk for breast cancer in the few women using glargine or NPH for >2 years (HR 0.67 [0.18–2.54]). The corresponding HRs for the other cancer outcomes are all close to 1.0, with the exception of >12–24 months and prostate cancer (2.66 [0.65–10.9]). This outlier result should be interpreted taking into account the absence of a monotonic pattern over duration of use and the small number and the unusually low incidence rate of prostate cancer in the NPH cohort.

In Table 4, we present the results of our two external validation studies to assess the role of various covariates not available in claims data. In both validation studies, BMI does not influence the choice between initiating long-acting insulin therapy with glargine versus NPH. These results were unaffected by controlling for other covariates in the propensity score model. The corresponding adjusted odds ratios for BMI (1-unit increase) and initiating glargine versus NPH were 1.00 (0.98–1.02) in the MGH cohort and 0.99 (0.96–1.03) in the Ochsner cohort.

All results were consistent when we restricted the patient population to those >40 years old and with prior use of oral antihyperglycemic agents (i.e., limited to patients with a very high probability of having type 2 diabetes), varied induction periods (i.e., excluding incident cancer cases for up to 12 month after insulin initiation), varied carryover effects (i.e., allowing for effects to carry on for up to 24 months or indefinitely after stopping treatment [first treatment carried forward or intention-to-treat analysis]), and excluded increasing proportions of those treated contrary to prediction (i.e., to assess the potential for bias assuming unmeasured confounding) (data not presented). For example, the following HRs were observed in the intention-to-treat analysis: 1.30 for breast cancer (0.83–2.05), 1.21 for prostate cancer (0.80–1.84), 0.97 for colon cancer (0.58–1.63), and 1.09 for any cancer (0.95–1.25).

CONCLUSIONS—In our large, new user, active comparator cohort study, we found no evidence that initiating patients with diabetes with insulin glargine leads to a higher risk of cancer compared with initiating similar patients on NPH. This result was consistent for overall and specific cancers (breast, prostate, colon) and a variety of sensitivity analyses addressing the relation of timing of insulin initiation with the risk for cancer (time after initiation, induction periods, lag times), subgroups, and the potential for unmeasured confounding by BMI and severity of diabetes.

A recent meta-analysis reported that there was no difference in the rates of breast cancer incidence in patients treated with insulin glargine compared with other formulations of insulin, but there was evidence for heterogeneity across studies (31). There are several studies that have suggested an increased risk of breast cancer (10–12,16). In particular, in a cohort of 15,227 women with type 2 diabetes followed for up to 8 years, breast cancer risk was not increased during the first 5 years of glargine use but there was a suggestion of increased risk among those with >5 years exposure (HR 1.8 [95% CI 0.8–40]). There was insufficient exposure among new users to examine those with ≥5 years of treatment. The results of two collaborating groups from Northern Europe and Kaiser Permanente were recently reported at 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 8–12 June 2012 (http://www.diabetes.org/for-media/2012/sci-sessions-insulin-cancer.html). Both studies reported an increased HR for breast cancer in the new user cohort with longer duration of treatment. Our study has the largest cohort of new users of glargine reported to date. The lack of an association among new users of glargine compared with new users of NPH for breast cancer, including those with treatment over 2 years, is reassuring, but further study of breast

Table 1—*Distribution of selected baseline characteristics in initiators of glargine and initiators of NPH and their effect on choice between initiating glargine versus NPH

	Actual cohorts		Effect on channeling, OR (95% CI)†	Weighted cohorts (%)‡	
	Glargine	NPH		Glargine	NPH
n	43,306	9,147			
Age (years), mean (SD)	61.3 (14.0)	58.9 (17.2)	1.001 (0.999–1.003)	61.0 (14.3)	61.5 (15.5)
Sex					
Male	20,369 (47.0)	3,611 (39.5)	1.29 (1.22–1.37)	45.8	45.7
Female	22,937 (53.0)	5,536 (60.5)	1.00 (reference)	54.2	54.3
Cohort year					
2004	528 (1.2)	362 (4.0)	0.29 (0.25–0.34)	1.7	1.7
2005	1,558 (3.6)	662 (7.2)	0.48 (0.43–0.53)	4.3	4.2
2006	2,435 (5.6)	948 (10.4)	0.56 (0.51–0.62)	6.4	6.3
2007	5,984 (13.8)	1,395 (15.3)	0.88 (0.82–0.95)	14.1	13.9
2008	12,640 (29.2)	2,685 (29.4)	1.00 (reference)	29.2	28.7
2009	12,109 (28.0)	1,925 (21.1)	1.28 (1.20–1.37)	26.8	27.5
2010	8,052 (18.6)	1,170 (12.8)	1.42 (1.31–1.53)	17.6	17.7
Medications					
ACE inhibitors	18,773 (43.4)	3,498 (38.2)	0.94 (0.89–0.99)	42.5	43.6
Anticholinergics	713 (1.7)	156 (1.7)	0.93 (0.77–1.13)	1.7	1.6
Antidepressants	11,028 (25.5)	2,062 (22.5)	1.18 (1.12–1.25)	25.0	26.4
ARBs	5,656 (13.1)	851 (9.3)	1.16 (1.07–1.26)	12.4	12.8
β-Blockers	15,678 (36.2)	2,842 (31.1)	0.98 (0.93–1.04)	35.4	36.6
β2-agonists	4,559 (10.5)	984 (10.8)	0.98 (0.90–1.07)	10.6	11.1
Bile acid sequestrants	237 (0.6)	43 (0.5)	1.01 (0.72–1.41)	0.5	0.5
Calcium channel blockers	9,813 (22.7)	1,826 (20.0)	0.97 (0.92–1.04)	22.2	23.2
Cholesterol absorption inhibitors	1,454 (3.4)	190 (2.1)	1.26 (1.07–1.47)	3.1	3.5
Digoxin	1,978 (4.6)	334 (3.7)	1.18 (1.04–1.34)	4.4	4.8
Estrogen	904 (2.1)	346 (3.8)	0.96 (0.79–1.16)	2.4	2.3
Fibrates	4,238 (9.8)	707 (7.7)	0.98 (0.89–1.06)	9.4	9.5
Loop diuretics	8,722 (20.1)	1,690 (18.5)	0.96 (0.89–1.03)	19.9	21.5
Metformin	27,347 (63.2)	4,544 (49.7)	1.26 (1.19–1.33)	60.8	61.2
Niacin	810 (1.9)	108 (1.2)	1.14 (0.93–1.41)	1.8	1.7
Nonloop diuretics	7,684 (17.7)	1,397 (15.3)	1.04 (0.97–1.11)	17.4	18.2
Oral contraceptives	593 (1.4)	317 (3.5)	0.71 (0.56–0.90)	1.7	1.6
Other diabetes drugs	9,416 (21.7)	891 (9.7)	1.87 (1.73–2.01)	19.7	21.4
Progestins	407 (0.9)	145 (1.6)	1.13 (0.89–1.45)	1.0	1.0
Statins	23,874 (55.1)	3,792 (41.5)	1.17 (1.11–1.23)	52.8	54.0
Sulfonylureas	28,399 (65.6)	4,443 (48.6)	1.57 (1.49–1.65)	62.7	64.4
Testosterone	250 (0.6)	30 (0.3)	1.42 (0.96–2.11)	0.5	0.6
Theophyline	275 (0.6)	44 (0.5)	1.39 (1.00–1.94)	0.6	0.7
Thiazolidinediones	14,085 (32.5)	1,954 (21.4)	1.46 (1.38–1.55)	30.6	31.8
Comorbidities					
Congestive heart failure	8,074 (18.6)	1,645 (18.0)	1.01 (0.93–1.09)	18.6	19.6
Diabetic nephropathy	11,432 (26.4)	2,345 (25.6)	0.90 (0.84–0.95)	26.3	27.6
Diabetic neuropathy	9,998 (23.1)	2,110 (23.1)	0.86 (0.81–0.91)	23.1	23.7
Diabetic retinopathy	11,613 (26.8)	2,364 (25.8)	0.94 (0.89–1.00)	26.7	26.8
Hypertension	35,314 (81.6)	6,842 (74.8)	1.13 (1.06–1.20)	80.5	81.7
Pulmonary infection	10,642 (24.6)	2,344 (25.6)	0.98 (0.92–1.05)	24.8	25.9
Health care use					
Hospitalizations (any reason)					
1	8,961 (20.7)	1,922 (21.0)	1.17 (1.07–1.29)	20.8	21.9
2	3,144 (7.3)	662 (7.2)	1.15 (1.03–1.28)	7.3	7.6
≥3	2,512 (5.8)	515 (5.6)	1.25 (1.11–1.42)	5.8	6.5
Days in hospital (any reason)					
1–2	2,794 (6.5)	618 (6.8)	0.92 (0.82–1.04)	6.5	6.6
3–5	4,251 (9.8)	913 (10.0)	0.95 (0.86–1.06)	9.9	10.3

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Table 1—*Continued*

	Actual cohorts		Effect on channeling, OR (95% CI)†	Weighted cohorts (%)‡	
	Glargine	NPH		Glargine	NPH
Physician encounters					
1–3	6,014 (13.9)	1,368 (15.0)	1.01 (0.88–1.15)	14.1	14.0
4–6	9,429 (21.8)	1,934 (21.1)	0.96 (0.84–1.09)	21.7	21.3
≥7	26,269 (60.7)	5,494 (60.1)	0.90 (0.79–1.02)	60.6	61.0
ED visits					
1	9,017 (20.8)	1,965 (21.5)	0.94 (0.88–1.00)	21.0	21.8
2	3,819 (8.8)	810 (8.9)	1.00 (0.91–1.09)	8.8	9.4
≥3	4,418 (10.2)	1,009 (11.0)	0.94 (0.86–1.04)	10.3	10.7
Screening tests					
Prostate-specific antigen	7,862 (38.6)	1,274 (35.3)	0.97 (0.90–1.06)	38.1	37.6
Mammography	7,138 (31.1)	1,215 (22.0)	1.59 (1.47–1.72)	29.5	31.5
Endoscopy	3,843 (8.9)	694 (7.6)	1.07 (0.98–1.16)	8.7	9.3
PAP smear	4,410 (19.2)	1,617 (29.2)	0.55 (0.51–0.60)	21.0	19.2
Blood lipid	31,583 (72.9)	5,992 (78.8)	1.21 (1.15–1.28)	71.7	72.1
ECG	22,770 (52.6)	4,575 (50.0)	1.08 (1.02–1.14)	52.2	53.9

Data are *n* (%) unless otherwise indicated. ARB, angiotensin receptor blocker; ECG, electrocardiogram; ED, emergency department; OR, odds ratio. *Initiation defined as no dispensed prescriptions for insulin during the 19 months before the first insulin prescription (with the exception of one prescription for a short-acting insulin) and filling a second prescription of the same insulin (glargine or NPH) within 6 months after the first prescription. †Channeling between initiation of glargine and initiation of NPH; ORs from multivariable logistic regression model including all covariates presented in the table (i.e., the propensity score model); ORs >1.0 indicate more likely to be initiated on glargine than NPH. ‡Pseudopopulation weighted by the IPTW to assess the performance of the propensity score to balance covariates (and therefore control for confounding) in the pseudopopulation.

cancer risk with long-standing glargine use is necessary.

We used duration of treatment as a proxy for cumulative dose. We could have used a measure of cumulative dose instead but, based on the small number of NPH initiators and the potential for time-varying confounding, opted to focus on the duration of treatment irrespective of dose analysis.

We combined the new user design with an active comparator cohort. Rather than comparing treated with untreated, this design allowed us to address a clinically more important question: If I need to initiate insulin therapy in my patients with diabetes, does choosing insulin glargine over NPH increase the risk for cancer? Results of studies using active comparators, while answering clinically more important questions, are inherently dependent on the comparator chosen. We chose NPH insulin as a comparator because *1*) most guidelines provide NPH insulin as the alternative to long-acting basal analog insulins like glargine and *2*) there is insufficient exposure to other long-acting analog insulins in the U.S.

Compared with patients initiating NPH, patients initiating glargine were

Table 2—*Initiation of long-acting insulin treatment and cancer incidence**

Cancer type and treatment	*N*	Events	Total person-years†	Incidence (per 100,000 person-years)	Unadjusted HR (95% CI)‡	Adjusted HR (95% CI)‡§
Breast‖						
Glargine	22,936	103	26,277	392	1.22 (0.75–2.00)	1.07 (0.65–1.75)
NPH	5,536	19	5,885	323	1.00 (reference)	1.00 (reference)
Prostate¶						
Glargine	20,298	119	24,208	494	1.02 (0.64–1.63)	1.19 (0.73–1.94)
NPH	3,602	20	4,116	486	1.00 (reference)	1.00 (reference)
Colon#						
Glargine	43,290	62	50,530	123	0.77 (0.44–1.33)	0.89 (0.49–1.60)
NPH	9,145	16	10,010	160	1.00 (reference)	1.00 (reference)
Any cancer						
Glargine	43,306	993	50,548	1,965	1.11 (0.95–1.30)	1.12 (0.95–1.32)
NPH	9,147	178	10,011	1,778	1.00 (reference)	1.00 (reference)

*Initiation defined as no dispensed prescriptions for insulin during the 19 months before the first insulin prescription (with the exception of one prescription for a short-acting insulin) and filling a second prescription of the same insulin (glargine or NPH) within 6 months after the first prescription. †As-treated analysis: patients stopping, switching, or augmenting their corresponding baseline treatment are censored at that point in time; median duration of follow-up 0.9 years in the glargine cohort and 0.8 years in the NPH cohort. ‡HRs (95% CI) from Cox proportional hazards models for the various cancer outcomes with baseline treatment as the only independent covariate. §Adjusted for all variables presented in Table 1 using IPTW. ‖Women only; women with prophylactic unilateral or bilateral mastectomy at the index prescription excluded. ¶Men only; men with partial or complete prostatectomy for any reason at the index prescription excluded. #Patients with prophylactic partial or complete removal of the colon at the index prescription excluded.

Table 3—*Initiation of long-acting insulin treatment and cancer incidence by duration of treatment

Cancer, time stratum, and treatment	Events	*N*	Total person-years†	Incidence (per 100,000 person-years)	Unadjusted HR (95% CI)‡	Adjusted HR (95% CI)‡§
Breast‖						
0 to <6 months						
Glargine	22,936	37	9,552	387	1.27 (0.57–2.85)	0.99 (0.46–2.13)
NPH	5,536	7	2,296	305	1.00 (reference)	1.00 (reference)
6 to <12 months						
Glargine	18,979	29	7,301	397	2.23 (0.68–7.33)	1.50 (0.52–4.31)
NPH	4,609	3	1,667	180	1.00 (reference)	1.00 (reference)
12 to <24 months						
Glargine	10,910	26	6,655	391	0.84 (0.35–2.04)	1.09 (0.38–3.12)
NPH	2,214	6	1,277	470	1.00 (reference)	1.00 (reference)
≥24 months						
Glargine	3,576	11	2,770	397	0.88 (0.24–3.27)	0.67 (0.18–2.54)
NPH	735	3	645	465	1.00 (reference)	1.00 (reference)
Prostate¶						
0 to <6 months						
Glargine	20,298	45	8,531	528	0.98 (0.46–2.07)	1.07 (0.51–2.23)
NPH	3,602	8	1,468	545	1.00 (reference)	1.00 (reference)
6 to <12 months						
Glargine	17,092	30	6,626	453	0.83 (0.35–2.00)	0.97 (0.41–2.31)
NPH	2,909	6	1,103	544	1.00 (reference)	1.00 (reference)
12 to <24 months						
Glargine	9,907	32	6,105	524	1.78 (0.54–5.80)	2.66 (0.65–10.9)
NPH	1,627	3	1,019	294	1.00 (reference)	1.00 (reference)
≥24 months						
Glargine	3,407	12	2,946	407	0.74 (0.22–2.48)	0.87 (0.21–3.65)
NPH	570	3	526	570	1.00 (reference)	1.00 (reference)
Colon#						
0 to <6 months						
Glargine	43,290	23	18,105	127	0.96 (0.37–2.53)	0.80 (0.33–1.95)
NPH	9,145	5	3,767	133	1.00 (reference)	1.00 (reference)
6 to <12 months						
Glargine	36,113	17	13,940	122	0.69 (0.25–1.88)	0.90 (0.30–2.75)
NPH	7,525	5	2,773	180	1.00 (reference)	1.00 (reference)
12 to <24 months						
Glargine	20,834	16	12,769	125	0.58 (0.21–1.57)	1.03 (0.28–3.85)
NPH	3,846	5	2,298	218	1.00 (reference)	1.00 (reference)
≥24 months						
Glargine	6,987	6	5,716	105	1.18 (0.14–9.76)	0.92 (0.10–8.49)
NPH	1,306	1	1,172	85	1.00 (reference)	1.00 (reference)
Any cancer						
0 to <6 months						
Glargine	43,306	392	18,112	2,164	1.14 (0.88–1.46)	1.11 (0.86–1.42)
NPH	9,147	72	3,767	1,911	1.00 (reference)	1.00 (reference)
6 to <12 months						
Glargine	36,125	259	13,945	1,857	1.04 (0.77–1.41)	1.14 (0.83–1.57)
NPH	7,526	50	2,774	1,803	1.00 (reference)	1.00 (reference)
12 to <24 months						
Glargine	20,842	242	12,773	1,895	1.12 (0.80–1.57)	1.06 (0.75–1.49)
NPH	3,846	39	2,298	1,697	1.00 (reference)	1.00 (reference)
≥24 months						
Glargine	6,989	100	5,718	1,749	1.21 (0.73–2.01)	1.34 (0.74–2.41)
NPH	1,306	17	1,172	1,451	1.00 (reference)	1.00 (reference)

*Initiation defined as no dispensed prescriptions for insulin during the 19 months before the first insulin prescription (with the exception of one prescription for a short-acting insulin) and filling a second prescription of the same insulin (glargine or NPH) within 6 months after the first prescription. †As-treated analysis: patients stopping, switching, or augmenting their corresponding baseline treatment are censored at that point in time; median duration of follow-up 0.9 years in the glargine cohort and 0.8 years in the NPH cohort. ‡HRs (95% CI) from Cox proportional hazards models for the various cancer outcomes with baseline treatment as the only independent covariate. §Adjusted for all variables presented in Table 1 using IPTW. ‖Women only; women with prophylactic unilateral or bilateral mastectomy at the index prescription excluded. ¶Men only; men with partial or complete prostatectomy for any reason at the index prescription excluded. #Patients with prophylactic partial or complete removal of the colon at the index prescription excluded.

generally more likely to have filled prescriptions for metformin, sulfonylureas, thiazolidinediones, and other diabetes drugs during the 12 months before initiating insulin. Glargine initiators were also more likely to have filled prescriptions for statins, have blood lipids tested, and have had a mammography, suggesting that glargine initiators are more likely to follow guidelines of disease prevention, i.e., healthy users (32). We successfully balanced the cohorts of glargine and NPH initiators on all these factors using propensity scores.

Our study has to be interpreted in the context of its limitations. While our study contributes considerably to the evidence base for longer-term treatment with glargine, our data on treatment beyond 2 years are limited. This limitation was mainly a function of patients not using insulin glargine (or NPH) over prolonged periods of time rather than lack of long-term observation of patients. This highlights actual dynamics in the treatment of patients with insulin. Of note, these actual dynamics also affect other studies, including the Hemkens et al. (1) study that reported an increase in cancer risk early after initiation of glargine treatment, and thus cannot explain the discrepancies in results observed. While all patients in our cohort initiated long-acting insulin after a period of at least 19 months without insulin use, some patients may have used insulin prior to that period and then stopped. We found ~100 out of the 52,453 patients meeting new use criteria more than once, indicating that new use equates to initiation for the great majority of patients. While health care claims data include prospective, longitudinal records of almost all dispensed prescriptions and are therefore almost ideal to track drug exposures (32), they are limited with respect to their sensitivity and specificity to detect cancer and capturing potentially important covariates. We used an algorithm with high specificity to define incident cancer (28) because a high specificity limits bias of ratio estimates (33).

We used two external validation studies to assess the potential for unmeasured confounding by BMI (34) and could show that BMI does not affect the decision to initiate insulin treatment with glargine versus NPH. Given that we observed similar patterns in two distinct settings, we find it plausible that this finding is generalizable to our cohorts. We could not control for a wide variety of other covariates, including e.g., smoking and socioeconomic status. While smoking increases the risk for a wide variety of cancers, the potential for confounding by socioeconomic status is limited because the impact of income on cancer incidence is complex and far from strong. Our data include a variety of different health care plans with different copayment structures that could influence channeling, but it is reasonable to assume that health care plan membership would not be associated with cancer risk independent of the factors we controlled for in our analyses (e.g., age, sex, and various health care–seeking behaviors, e.g., screening examinations). To assess the potential for socioeconomic status affecting channeling, we stratified our new user cohorts by Medicaid versus commercially insured. Of all Medicaid beneficiaries initiating insulin therapy in 2010, 84.3% were initiated on glargine; the corresponding number was very similar (88.7%) in commercially insured patients, further limiting the potential for confounding. The number of patients initiated on NPH was much smaller than the number initiated on glargine in our study of U.S. patients with diabetes. While this reflects the reality of most patients being initiated on glargine rather than NPH in the U.S., it decreases the precision of our estimates, especially for long-term use. We therefore cannot exclude chance as an alternative explanation of our results.

Based on previous studies and the substantial contribution of our study, we conclude that there does not seem to be an increased risk for cancer, including breast cancer, after initiation of glargine compared with NPH in patients with (mostly type 2) diabetes. The current evidence on long-term use is limited, however, mainly based on the actual dynamic in insulin treatment in the "real world." While limiting our evidence base with respect to risk for cancer, this relative lack of empirically observed long-term use also limits the hypothetical potential for negatively affecting public health. As always, physicians should weigh potential benefits and harms when making treatment decisions.

Table 4—*Effect of BMI on channeling between initiating glargine versus initiating NPH: external validation studies*

	Glargine	NPH
MGH		
n	574	412
BMI (kg/m^2), mean ± SD*	32.7 ± 7.53	32.4 ± 8.43
BMI (kg/m^2), *n* (%)		
<19	4 (0.7)	8 (1.9)
19 to <25	77 (13.4)	67 (16.3)
25 to <30	150 (26.1)	105 (25.5)
30 to <35	146 (25.4)	104 (25.2)
35 to <40	114 (19.9)	64 (15.5)
40 to <45	45 (7.8)	36 (8.7)
≥45	38 (6.6)	28 (6.8)
Ochsner		
n	1,155	127
BMI (kg/m^2), mean ± SD	34.8 ± 8.2	35.9 ± 8.4
BMI (kg/m^2), *n* (%)		
<19	2 (0.2)	0 (0.0)
19 to <25	90 (7.8)	12 (9.4)
25 to <30	267 (23.1)	19 (15.0)
30 to <35	313 (27.1)	33 (26.0)
35 to <40	239 (20.7)	27 (21.3)
40 to <45	130 (11.3)	18 (14.2)
≥45	114 (9.9)	18 (14.2)

*BMI calculated as weight in kilograms divided by the square of height in meters; according to WHO, a BMI between 25 and 30 kg/m^2 is overweight and a BMI >30 kg/m^2 is obese.

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Final decisions regarding design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and submission of the manuscript were the sole responsibilities of the authors.

T.S. participated in study conception and design, participated in the acquisition of data, participated in the analysis and interpretation of data, wrote the first draft of the manuscript, and reviewed and provided comments on the manuscript. M.A.M. participated in the acquisition of data, participated in the analysis and interpretation of data, and reviewed and provided comments on the manuscript. H.Z. participated in the analysis and interpretation of data and reviewed and provided comments on the manuscript. J.B.M., S.L., and L.B. participated in the acquisition of data, participated in the analysis and interpretation of data, and reviewed and provided comments on the manuscript. E.M. participated in the analysis and interpretation of data and reviewed and provided comments on the manuscript. R.W. participated in the acquisition of data, participated in the analysis and interpretation of data, and reviewed and provided comments on the manuscript. L.M.L. participated in study conception and design, participated in the acquisition of data, participated in the analysis and interpretation of data, and reviewed and provided comments on the manuscript. V.P. participated in the acquisition of data, participated in the analysis and interpretation of data, and reviewed and provided comments on the manuscript. J.B.B. participated in study conception and design, participated in the acquisition of data, participated in the analysis and interpretation of data, and reviewed and provided comments on the manuscript. T.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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